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Moderate to Severe Crohn's Disease: Are We Treating Successfully?

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By

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INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease for which several medical therapies are currently available. Despite the significant untoward side effects of systemic corticosteroids, these drugs are typically initiated before a trial of a more gut-specific biologic treatment such as a recombinant humanized monoclonal antibody or anti-tumor necrosis factor (TNF) antibody. Because there are currently no evidence-based guidelines for the treatment moderate-to-severe (MTS) CD, expert opinion largely forms the guidelines by which we initiate corticosteroids and then follow with trials of biologics. Current conventional guidelines follow a 'step care' or 'step ladder' plan which is an incremental approach in which corticosteroids and immunosuppressants are started sequentially. However, this approach does not prevent disease progression and demonstrates an important risk of adverse events from repeated courses of corticosteroids.[1]

Crohn's Disease consists of phases of relapse and remission. A clinician's objective is to induce and maintain remission of CD, which is currently defined as complete mucosal healing identified via endoscopic evaluation, and normalization of serological activity indexes, including c-reactive protein and erythrocyte sedimentation rate.[2] The course and severity of CD, often measured using the Crohn's disease activity index (CDAI),[3,4] differs from one patient to another. The CDAI is widely used to asses severity, medication efficacy and remission in patients with CD. Scores can range from zero to over 600 and are based on patient reported information, using a seven-day diary, as well as other measurements including a patient's weight and hematocrit. If a patient has a score of greater than 220 it is defined as moderate to severe disease with a score of greater than 300 representing severe disease. Remission is reached when a patient has a CDAI score of less than 150. Many research studies are classifying medication response as a reduction in the CDAI of greater than 70 points. However, this could be confusing if clinicians are trying to establish guidelines which include complete mucosal healing, which is not noted on the CDAI. It also does not account for medications tried or failed, therefore a patient's CDAI score may not calculate into the proper category when in fact they have corticosteroid-refractory, moderate-to-severe CD.[5] Therefore, a clearer guideline is needed for patients with corticosteroid-refractory moderate-to-severe CD.

Population-based data from 1935-2008 shows that only 10% of patients with CD will have prolonged clinical remission. Of all patients diagnosed with CD, 50% of patients will have an intestinal complication within 20 years after diagnosis. It is estimated that about 20% of CD patients will be admitted to the hospital at least annually and 50% of the patients will require intestinal surgery 10 years after diagnosis. [6]

There are many medications indicated for the treatment of CD. Selection should aim to balance side-effects and long-term complications. The initial choice in medication treatment should also incorporate the individual profile of the patient as well making more potent medications available to higher risk patients instead of the standard stepwise approach.[6] While the immunosuppressive medications azathioprine, 6-mercaptopurine and methotrexate are corticosteroid-sparing, they are not highly effective at mucosal healing or disease prevention. Because of this factor, immunosuppressive medications were not directly compared in this review.[1]

THE USE OF CORTICOSTEROIDS IN CROHN'S DISEASE

Corticosteroid therapy has been a gold-standard medication in the treatment of CD for acute attacks and is often the initial treatment for newly diagnosed patients. Current guidelines recommend that patients with active disease be treated with corticosteroid therapy. The recommendation is currently written as corticosteroids for first line therapy with treatment time limited at 3-4 months as patients could start experiencing toxic effects at treatments greater than 6 months.[7] However, steroid use is associated with injurious systemic effects, bone loss, and medication interactions, and patients become dependent on these medications to keep their disease controlled.

A recent study by T. Molnar et al. revealed that initiating steroids as the first line of treatment causes faster relapse in some patients. One group of MTS CD patients who initiated steroids at the time of diagnosis, and subsequently started on a biologic, only achieved remission for one year or less. Other patients who were not started on steroids prior to initiation of biologics stayed in remission longer.[3] Therefore, corticosteroids are effective at initiating, but not maintaining, a state of remission. Moreover, many patients who respond to

corticosteroids become dependent on therapy and therefore cannot be weaned off, resulting in a true failure of clinical remission.[8]

Extended exposure to corticosteroid treatment is also associated with the complications of Cushing's syndrome and therefore an increased risk of mortality. Some practitioners have chosen to forgo the use of corticosteroids altogether, to reduce the risk of the aforementioned risks, and use instead corticosteroid-sparing drugs such as azathioprine, mercaptopurine or methotrexate. The issue with these immunosuppressive drugs is that they are not recommended to be started in the earlier course of the disease. This is why it is so important to bring biologics to the forefront of the battle against CD.[7]

INFLIXIMAB

Infliximab (Remicade), a tumor necrosis factor alpha (TNF-α), is a proinflammatory cytokine that has an important role in the pathogenesis of inflammatory bowel disease, and more specifically CD.[4] Infliximab is a chimeric anti-TNFα monoclonal antibody which binds to TNFα with high affinity, thereby neutralizing its biological activity.[4] Current guidelines, as noted above, recommend concomitant use of a thiopurine analog with scheduled Infliximab (IFX) for the induction and maintenance of remission in MTS CD.[10] This approach to therapy was adapted from the treatment of Rheumatoid arthritis (RA) for patients at high risk of disease progression. It uses the 'top-down' approach using methotrexate with a TNF antagonist. The concept driving this combination is the recognition that combined therapy is more effective than monotherapy.[1]

Neutralization of TNF has been shown to decrease recruitment of inflammatory cells and granuloma formation in several animal models. One study's aim was to investigate the safety and potential efficacy of an anti-TNF monoclonal antibody in the treatment of active CD in patients with steroid-refractory disease.[9] The study consisted on ten patients with an age range of 20-64 years and each patient was considered to have active CD based on CDAI with a mean score of 258; representing moderate to severe disease. Treatment consisted of a single intravenous infusion of the anti TNF at a dose of 10 mg/kg and two patients were selected to receive 20 mg/kg to evaluate the safety at a higher dose. Drug therapies were continued for a

two months span which included the whole study period. Videoendoscopy of the colon was performed one day before the infusion and at weeks four and eight. One patient was excluded from the study because the CDAI could not be verified. Nine patients remained in the study and of those nine, eight reported improvement in subjective symptoms within one week after treatment. Four weeks after infusion these same eight patients scored "excellent or good response to treatment" on the subjective scoring list. At the beginning of the study the mean CDAI study was 257 before treatment and decreased to 114 at two weeks into the study, 79 at four weeks, 61 at six weeks and 69 at week eight. The study provides evidence that TNF-α is a major factor in the pathophysiology of CD.[9] This study was not designed to show the long-term efficacy of anti-TNF nor did it look at maintenance of remission; this study was small and uncontrolled and therefore, longer controlled, trials will need to be performed.

Some patients with MTS active CD will not have a response to TNF antagonists available, and the trial of a second TNF antagonist decreases the efficacy of the second drug compared to a patient who has never received a TNF antagonist. This is where veldolizumab comes into the picture.[13]

VEDOLIZUMAB

Vedolizumab (Entyvio) is a humanized α4β7 integrin, immunoglobulin G1 monoclonal antibody. Its selective inhibition allows for inhibition of the α4β7/MAdCAM-1 pathway and should ameliorate gastrointestinal inflammation without inhibiting systemic immune responses or affecting T-cell trafficking to the CNS. A randomized, placebo-controlled, double-blind, multinational, multicenter trial named the GEMINI looked to determine the effects of vedolizumab induction therapy on clinical remission. The third phase of this trial, initiated in November 2010 and completed in April 2012, showed an increase in remission rates from weeks six to ten in the overall study population while sparing these patients of the effects of corticosteroids. These findings support the safety of vedolizumab in patients with CD and are consistent with the drug's postulated gut-selective mechanism of action.[12]

COST AND BENEFIT

Prior to the emergence of biologic medical therapy, MTS CD patients suffered increased hospitalization rates; furthermore, 40-50% of patients required surgery within 10 years from the time of diagnosis. More recently, data from Kaiser Permanente in Canada and Northern California reveal that biologic medical therapy has helped decrease hospitalizations rates in patients with MTS CD. In addition, a Manitoba Canada study reported reduced surgery rates in the post-biologic induction period and a decreased postoperative recurrence about 50% after 10 years.[11] Despite these advances, many patients cannot afford the high cost of these new medications. A recent technical review by the American Gastroenterological Association Institute reported annual treatment costs of $8265 per patient, extrapolating to yearly costs of $2.5 to $4 billion for the American population with CD.[13]

RECOMMENDATIONS

The official recommendations of the American Gastroenterological Association Institute (AGA) include using Anti-TNF-α Drugs to induce remission in patients with MTS CD, reporting with strong recommendation and Moderate-Quality Evidence grade. Evidence shows that the anti-TNF-α drugs infliximab or adalimumab are more likely than the placebo to induce remission in patients with MTS CD refractory to other therapies including corticosteroids.[13] However, there is no recommendation for the use of biologics alone to maintain clinical remission in patients with MTS CD.

One main issue with current guidelines for MTS CD is that they focus on managing acute flares and then managing the maintenance of clinical remission, instead of clinical remission being the primary focus. Use of corticosteroids remains first-line therapy for acute flare-ups and then reserving immunosuppressive agents for patients who develop corticosteroid dependency.[1] There is no real guideline or recommendation as to when a TNF-α or humanized α4β7 integrin, immunoglobulin G1 monoclonal antibody can be initiated in patients with MTS CD in the presence of early disease and to maintain remission.

SUMMARY

As it stands today, corticosteroids are initiated for an acute attack or a new diagnosis for a patient with CD. Biologics such as Entyvio or Remicade are started later, with the hope of steroid-free disease remission. Studies have shown that clinical deep remission without steroid use is possible using biologics, and these drugs can be used as maintenance therapy as well. Often, the most common treatment regimen for patients with corticosteroid-refractory MTS CD involves choosing a thiopurine, an anti TNF- monoclonal antibody, or both.[10] Many clinical trials have been completed to assess efficacy which was published in a review article by Côté-Daigneault et al. and is laid out in the table below.[17]

Table 1. Biologics trials evidences in Crohn's disease

	Induction	Maintenance	Fistulizing	Mucosal healing	Combination thiopurine	Combination methotrexate	Rescue[a]
Anti-TNF alpha							
Infliximab	+	+	+	+	+	−	NA
Adalimumab	+	+	+	+	+/−	NA	+
Certolizumab	+	+	+	#	NA	NA	+
Golimumab	NA	NA	NA	NA	NA	NA	NA
Anti-integrin							
Natalizumab	+	+	NA	NA	NA	NA	NA
Vedolizumab	+	+	NA	NA	NA	NA	+
Others							
Ustekinumab (phase IIb)	+	+	NA	NA	NA	NA	+

[a]Efficacy of the treatment in patients who have failed previous biologics treatment.
NA: Study is not available.
+: Study is available with a positive outcome.
−: Study is available with a negative outcome.
+/−: Retrospective studies.
#: Study with a positive outcome but not comparing with placebo.

Cheifetz AS, Feuerstein JD. *Treatment of inflammatory bowel disease with biologics.* 1st ed. 2018 ed. Cham: Springer Verlag; 2018:420-428. https://ebookcentral.proquest.com/lib/[SITE_ID]/detail.action?docID=5143365. 10.1007/978-3-319-60276-9

Unfortunately, only a limited number of trials have been performed to demonstrate the effectiveness of the recombinant humanized monoclonal antibody Vedolizumab, and the anti-TNF antibody Infliximab in induction/maintenance of remission of corticosteroid-refractory moderate-to-severe inflammatory bowel disease. More extensive research will help to change treatment guidelines as a whole and will help to determine the exact patient population who

would benefit from starting a biologic as the first line of treatment. This will also help to determine if corticosteroids should be initiated at all, especially since the goal is complete mucosal healing and clinical remission free of corticosteroid therapy.

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